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Matthieu Raynal, François Portier, Piet W. N. M. Van Leeuwen, Laurent Bouteiller. Tunable Asymmetric Catalysis through Ligand Stacking in Chiral Rigid Rods. *Journal of the American Chemical Society*, 2013, 135 (47), pp.17687–17690. 10.1021/ja408860s. hal-01696696

HAL Id: hal-01696696

<https://hal.science/hal-01696696>

Submitted on 29 Sep 2020

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Tunable asymmetric catalysis through ligand stacking in chiral rigid rods.

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Supporting Information Placeholder

ABSTRACT: Chiral benzene-1,3,5-tricarboxamide (BTA) ligands, comprising one diphenylphosphino group and one or two remote chiral 1-methylheptyl side chains, were evaluated in the rhodium-catalyzed asymmetric hydrogenation of dimethyl itaconate. Despite the fact that the rhodium atom and the chiral center(s) are separated by more than 12 covalent bonds, up to 82% ee was observed. A series of control and spectroscopic experiments confirmed that the selectivity arises from the formation of chiral helical polymers by self-association of the BTA monomers through non-covalent interactions. The addition of a phosphine-free chiral BTA, acting as a co-monomer for the chiral BTA ligands, increases the level of enantioselectivity (up to 88% ee). It illustrates how the selectivity of the reaction can be increased in a simple fashion by mixing two different BTA monomers. The concept was further probed by performing the same experiment with an achiral BTA ligand, *i.e.* a phosphine-functionalized BTA that contains two remote octyl side chains. It afforded an encouraging 31% ee, thus demonstrating the catalytically relevant transfer of chirality between the self-assembled units. It constitutes a unique example of the sergeants-and-soldiers principle applied to catalysis.

In Nature, the combination of local chiral centers and recognition elements leads to the formation of supra-macromolecular chiral assemblies such as the right-handed double helical structure of DNA (B-DNA) and the complex secondary structure of proteins. These highly ordered architectures furnish a well-defined chiral environment that can be used as a scaffold for the development of non-natural reactions. To this end, efficient asymmetric hybrid catalysts¹ have been constructed that combine a metal and proteins² or DNA-scaffolds.³

An important challenge that remains is the development of asymmetric metal catalysts based on a scaffold that can be easily constructed and modified. Catalysts have recently been developed that associate a metal center and a chiral module in the same supramolecule, however the relative structural complexity of these systems make them difficult to modulate.^{4,5} In parallel, two main classes of asymmetric metal catalysts based on a covalent macromolecular scaffold have

been reported: (i) privileged ligands (mainly derived from BINOL and BINAP) embedded in a polymer backbone,⁶ and (ii) metal binding groups covalently attached to a chiral polymeric scaffold.⁷ To the best of our knowledge, only one example of an asymmetric metal catalyst based on an artificial supra-macromolecular scaffold has been reported. Liu and co-workers found that Cu²⁺ atoms do not disrupt the tubular self-assembly formed by a chiral bolaamphiphile gelator in water,⁸ and that the Cu²⁺ aligned at the surface of the nanotube worked as catalytic sites. The self-assembled catalyst provides 55% ee at best for a benchmark Diels–Alder cycloaddition, the sense of asymmetric induction being dictated by the chirality of the nanotube. It appears to us that the use of a supra-macromolecular chiral scaffold, resulting from the self-association of structurally simple sub-units, is a good strategy towards the development of a new class of asymmetric metal catalysts.

Among the large number of supramolecular polymers with a well defined helical structure,⁹ we focused on the benzene-1,3,5-tricarboxamide (BTA) moiety due to its well-known ability to generate helical rods through a combination of three-fold hydrogen bonds and π - π stacking interactions.¹⁰ Introduction of one remote chiral center as a side-chain of the BTA enables the formation of chiral helices with a single helical twist. Moreover, the chirality of the helices can be finely tuned because mixtures of BTA monomers follow the “majority rules”¹¹ and the “sergeants-and-soldiers” effects.¹² Herein, we demonstrate that phosphine-functionalized BTAs self-assemble into chiral helices, providing an efficient and tunable scaffold for asymmetric catalysis.¹³

A set of BTA ligands have been prepared (see the SI) that contain a central BTA ring connected to a 1,3-phenylenediphenylphosphino group and two alkyl side chains. The BTA ligands differ by the nature of the alkyl side chain (either chiral 1-methylheptyl or octyl) and the degree of substitution of the two alkyl amide functions. Chiral BTA ligands contain one or two remote chiral 1-methylheptyl side chains while achiral BTA ligands possess two peripheral octyl chains (see formulae and nomenclature in Chart 1). Our initial approach was to probe if chiral helices formed by self-assembled BTA ligands can be used as a catalytic platform for metal-catalyzed asymmetric reactions. Also we wondered whether the sergeants-and-soldiers principle can be applied

Chart 1. BTA derivatives used in this study and their nomenclature.

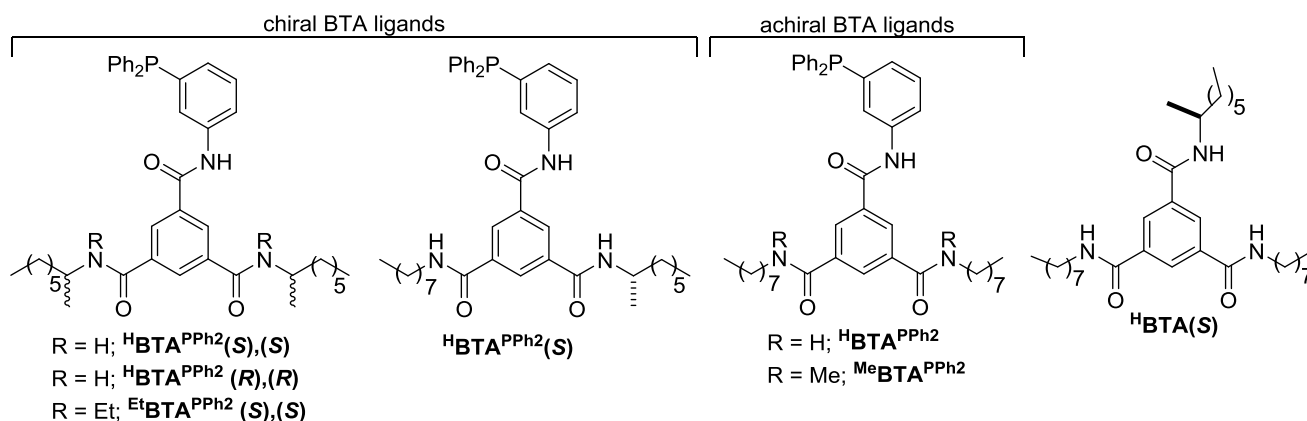
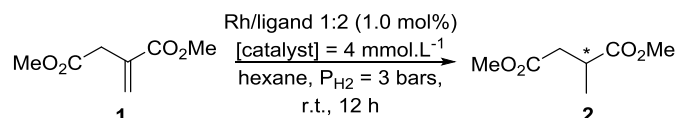


Table 1. Evaluation of the BTA ligands for the hydrogenation of **1**^a



Entry	BTA ligand	BTA additive	Rh precursor	ee (%)
1	${}^H\text{BTA}^{\text{PPh}_2}(\text{S}),(\text{S})$	-	[Rh(cod) ₂]BAR _F	82
2	${}^H\text{BTA}^{\text{PPh}_2}(\text{S})$	-	[Rh(cod) ₂]BAR _F	67
3	${}^H\text{BTA}^{\text{PPh}_2}(\text{R}),(\text{R})$	-	[Rh(cod) ₂]BAR _F	-81
4	${}^H\text{BTA}^{\text{PPh}_2}(\text{S}),(\text{S})$	-	[Rh(cod) ₂]BF ₄	15 ^b
5	${}^{\text{Et}}\text{BTA}^{\text{PPh}_2}(\text{S}),(\text{S})$	-	[Rh(cod) ₂]BAR _F	0
6	${}^{\text{Et}}\text{BTA}^{\text{PPh}_2}(\text{S}),(\text{S})$	${}^H\text{BTA}(\text{S})^c$	[Rh(cod) ₂]BAR _F	0
7	${}^H\text{BTA}^{\text{PPh}_2}(\text{S}),(\text{S})$	${}^H\text{BTA}(\text{S})^c$	[Rh(cod) ₂]BAR _F	88
8	${}^H\text{BTA}^{\text{PPh}_2}(\text{S})$	${}^H\text{BTA}(\text{S})^c$	[Rh(cod) ₂]BAR _F	86
9	${}^H\text{BTA}^{\text{PPh}_2}$	-	[Rh(cod) ₂]BAR _F	0
10	${}^H\text{BTA}^{\text{PPh}_2}$	${}^H\text{BTA}(\text{S})^c$	[Rh(cod) ₂]BAR _F	31
11	${}^{\text{Me}}\text{BTA}^{\text{PPh}_2}$	${}^H\text{BTA}(\text{S})^c$	[Rh(cod) ₂]BAR _F	0

^a Conversion 100%, the experiments were performed at least in triplicate (except for control experiments 4,5,6, 9,11). Standard deviation for the ee < 2% (entries 1,3,7,8), =5% (entry 10), =8% (entry 2). Positive value of ee corresponds to the (R) enantiomer according to reference 14 ^b Conversion 90%. ^c BTA additive (2.5 mol%). See SI for more details.

to catalysis in order to increase the selectivity of the resulting supramolecular catalysts. We chose the rhodium-catalyzed asymmetric hydrogenation of dimethyl itaconate (**1**) as a reaction of reference.

A short screening of the catalytic conditions (see the SI, Table S.1) helped us to identify the following satisfactory parameters: hexane as the solvent, a rhodium:ligand ratio of 1:2 and [Rh(cod)₂]BAR_F as the rhodium precursor. Because the rhodium atom and the chiral centers are separated by more than 12 covalent bonds, we were surprised to see that ${}^H\text{BTA}^{\text{PPh}_2}(\text{S}),(\text{S})$ alone provided the (R) enantiomer of **2** with 82% ee (Table 1, entry 1).⁵ Its enantiomer, ${}^H\text{BTA}^{\text{PPh}_2}(\text{R}),(\text{R})$, yielded the (S) enantiomer of **2** with the same selectivity (81% ee, entry 3). ${}^H\text{BTA}^{\text{PPh}_2}(\text{S})$, which contains only one

chiral side chain, was slightly less selective than ${}^H\text{BTA}^{\text{PPh}_2}(\text{S}),(\text{S})$ (67% ee, entry 2). As expected, the achiral phosphine ligand, ${}^H\text{BTA}^{\text{PPh}_2}$, provided no enantioselectivity for the catalytic reaction (entry 9). Consequently, additional catalytic experiments and structural studies were performed to check whether the selectivity observed arises from the formation of non-covalent interactions between the BTA monomers.

A first evidence of the key role played by non-covalent interactions on the enantioselectivity stems from the fact that ${}^{\text{Et}}\text{BTA}^{\text{PPh}_2}(\text{S}),(\text{S})$, for which two alkyl amide functions have been ethylated, gave no enantioselectivity for the reaction (Table 1, entry 5). The presence of a single N-H function (corresponding to the aryl amide function) instead of three N-H functions probably prevents the formation of the assemblies.¹⁵ Also, the enantioselectivity dropped when: (i) the solvent polarity was increased (the selectivity was low in toluene and totally lost in CH₂Cl₂, see Table S.2) and (ii) the hydrogen bond accepting ability of the rhodium counteranion was increased (compare BAR_F and BF₄, entry 1 and 4 respectively in Table 1). These experiments demonstrate that the observed selectivity for ${}^H\text{BTA}^{\text{PPh}_2}(\text{S}),(\text{S})$, ${}^H\text{BTA}^{\text{PPh}_2}(\text{S})$ and ${}^H\text{BTA}^{\text{PPh}_2}(\text{R}),(\text{R})$ is not due to isolated, dissociated chiral BTA ligands: it is related to the formation of chiral self-assemblies that results from hydrogen bonding interactions between the BTA units.

We then performed spectroscopic and scattering analyses to gain insight into the structure of the self-associated ${}^H\text{BTA}^{\text{PPh}_2}(\text{S}),(\text{S})$. We compared the spectroscopic signature of ${}^H\text{BTA}^{\text{PPh}_2}(\text{S}),(\text{S})$ and ${}^H\text{BTA}(\text{S})$ since the cooperative polymerization in alkanes of the latter has been fully assessed by Meijer, Palmans and co-workers.¹⁶ FTIR spectroscopy (Figure S.1) shows that both BTA derivatives are fully aggregated in decaline (4.0 mmol.L⁻¹), as shown by the frequency of the amide vibrations (3236 cm⁻¹, 1640 cm⁻¹ and 1555 cm⁻¹). Conversely, ${}^H\text{BTA}^{\text{PPh}_2}(\text{S}),(\text{S})$ is fully dissociated in CH₂Cl₂ at the same concentration (ν_{free N-H} = 3430 cm⁻¹, ν_{free C=O} = 1665 cm⁻¹, ν_{free amidell} = 1519 cm⁻¹). Moreover, small angle neutron scattering (SANS) analyses prove the formation of long aggregates for both ${}^H\text{BTA}(\text{S})$ and ${}^H\text{BTA}^{\text{PPh}_2}(\text{S}),(\text{S})$ in deuterated cyclohexane (at ca. 3 mmol.L⁻¹). The scattering curves (Figure S.2) are characterized by a q⁻¹ dependence at low angles representative of rigid cylindrical objects that are

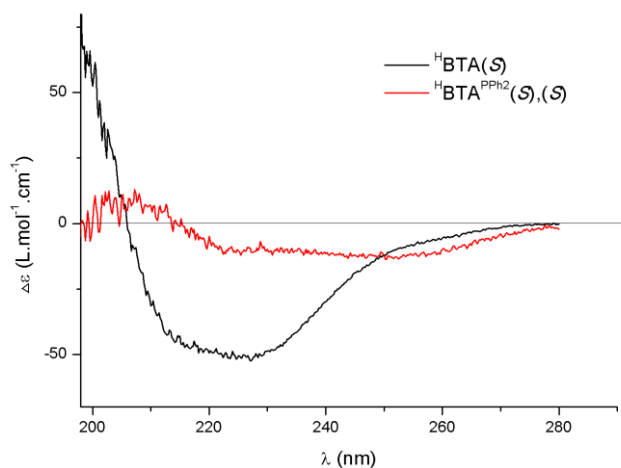


Figure 1. CD spectra of ${}^H\text{BTA}(\text{S})$ and ${}^H\text{BTA}^{\text{PPh}_2}(\text{S}),(\text{S})$ in decaline recorded at 298 K at a concentration of $30 \mu\text{mol}\cdot\text{L}^{-1}$.

longer than 200 \AA , i.e. at least 60 stacked BTAs. The data can be fitted¹⁷ using the form factor for rigid rods with a circular cross-section yielding radii of 10 and 9 \AA for ${}^H\text{BTA}(\text{S})$ and ${}^H\text{BTA}^{\text{PPh}_2}(\text{S}),(\text{S})$ respectively. Finally, the chiral nature of the self-assemblies was probed by circular dichroism (CD). The CD spectrum of ${}^H\text{BTA}^{\text{PPh}_2}(\text{S}),(\text{S})$ in decaline ($30 \mu\text{mol}\cdot\text{L}^{-1}$) shows a negative Cotton effect with two maxima at approximately 207 nm and 225 nm (Figure 1). The shape of the CD spectrum and the values of the molar ellipticity significantly differ from the one obtained with ${}^H\text{BTA}(\text{S})$ as a probable result of the additional presence of aromatic chromophores located on the phosphorus atom (see the UV-Vis spectra, Figure S.3) and/or a different conformation of the monomer within the chiral nanohelices.

The above analyses clearly demonstrate that ${}^H\text{BTA}^{\text{PPh}_2}(\text{S}),(\text{S})$ is able to form chiral helical polymers in alkanes. It proves that the presence of the phosphine does not significantly alter the formation of the self-assemblies that are typically observed with non-functionalized BTA derivatives. Investigation of the self-assembly behavior of the precatalyst, obtained by mixing two equiv. of ${}^H\text{BTA}^{\text{PPh}_2}(\text{S}),(\text{S})$ and one equiv. of $[\text{Rh}(\text{cod})_2]\text{BAR}_F$, is hampered by its very low solubility ($\ll 30 \mu\text{mol}\cdot\text{L}^{-1}$) in apolar solvents. However, control experiments performed for the catalytic reactions (see Table 1) support the formation of chiral assemblies for the precatalyst and/or the catalytically active species in hexane. Accordingly, we propose a helical polymeric structure for the precatalyst (see Figure 2); the catalytically active centers formed by the rhodium atoms linked to the phosphorous atoms are distributed along the scaffold of the helices formed by association of the BTA rings.¹⁸

The non-covalent nature and the one-dimensional structure of the catalytic system make it particularly easy to attempt to tune the selectivity of the reaction by adding a co-monomer. Therefore, a phosphorus-free chiral BTA, ${}^H\text{BTA}(\text{S})$, was combined with the previously mentioned chiral BTA ligands to examine whether the presence of this co-monomer affects the overall catalytic performance. ${}^H\text{BTA}(\text{S})$ (2.5 mol%) and the chiral BTA ligands (2.0 mol%) were combined together before the addition of $[\text{Rh}(\text{cod})_2]\text{BAR}_F$ (1.0 mol%). An increase of the selectivity was observed for both ${}^H\text{BTA}^{\text{PPh}_2}(\text{S}),(\text{S})$ and ${}^H\text{BTA}^{\text{PPh}_2}(\text{S})$, providing **2** with 88% ee (entry 7, Table 1) and 86% ee (entry 8) instead of 82% ee and 67% ee respectively in the absence of the additive. Such an increase in the selectivity was not observed with

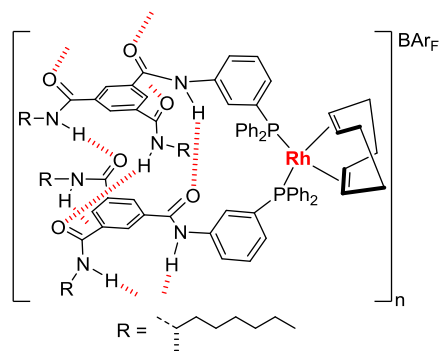


Figure 2. Proposed structure for the precatalyst derived from ${}^H\text{BTA}^{\text{PPh}_2}(\text{S}),(\text{S})$. n , the degree of polymerization, depends on the reaction conditions; it is probably high in hexane, giving rise to a selective catalyst and low in CH_2Cl_2 (non-selective catalyst).

${}^{\text{Et}}\text{BTA}^{\text{PPh}_2}(\text{S}),(\text{S})$ (entry 6) demonstrating that the incorporation of ${}^H\text{BTA}(\text{S})$ within the self-assemblies of ${}^H\text{BTA}^{\text{PPh}_2}(\text{S}),(\text{S})$ is at the origin of the improved catalytic performance. This blank experiment also shows that fortuitous coordination of the amides moieties to the rhodium could not explain the enhanced enantioselectivity observed.

As an ultimate test of the concept, catalytic experiments were performed by mixing an achiral BTA ligand (${}^H\text{BTA}^{\text{PPh}_2}$) and ${}^H\text{BTA}(\text{S})$. Although the observed selectivity was low (31% ee, entry 10) it clearly proves that ${}^H\text{BTA}(\text{S})$ is able to create a chiral environment for catalysis, although it does not directly interact with the rhodium atoms. Control experiments with ${}^{\text{Me}}\text{BTA}^{\text{PPh}_2}$, the analogue of ${}^H\text{BTA}^{\text{PPh}_2}$ with *N*-methylated alkyl amide functions, confirmed that the selectivity arises from the formation of a hydrogen-bonded copolymer between ${}^H\text{BTA}^{\text{PPh}_2}$ and ${}^H\text{BTA}(\text{S})$ (entry 11). The exact mechanism at the origin of the enhanced enantioselectivity observed with ${}^H\text{BTA}(\text{S})$ as an additive remains to be elucidated; however it can act as a co-monomer, improving the degree of the chiral amplification in a way that is reminiscent of the sergeants-and-soldiers principle occurring in both helical supramolecular¹⁹ and covalent polymers.²⁰

To conclude, the self-association of phosphine-functionalized BTA monomers that possess remote chiral groups provides supramolecular chiral helices; the chirality transfer between the helices and the catalytically active rhodium centers is sufficiently efficient to promote the asymmetric hydrogenation of dimethyl itaconate with good selectivity. The self-assemblies are based on non-covalent interactions (hydrogen bonding and π - π stacking) between structurally simple BTA units and can be modulated by incorporation of phosphorus-free monomers. Ongoing work in our laboratory encompasses a better understanding of the nature of the rhodium self-assemblies and the scope and limitations of this new class of catalysts.

ASSOCIATED CONTENT

Supporting Information

Experimental procedures, analytical data and spectral data for the new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

AUTHOR INFORMATION

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Notes

The authors declare no competing financial interests.

ACKNOWLEDGMENT

We are grateful to Ken Goeury for his experimental contribution to the project, Marta Serrano Torné for technical assistance, the ChromTAE unit of ICIQ for GC and HPLC analyses, Nicolas Vanthuyne (ISM2, Aix-Marseille Université) for chiral HPLC analyses and Christophe Desmarests (IPCM, UPMC) for access to the CD spectrometer. We thank François Boué (LLB, Saclay) for assistance with SANS experiments.

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